

Diminution of the Anti-PRP Response to a Combined DTaP/Hib Vaccine by Concurrent IPV Vaccination

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Pediatric Infectious Disease Journal, May 2000

VRBPAC - January 27, 2000

Sponsors / Sites

Sponsors: **CBER/FDA**

DMID/NIAID/NIH

Sites: **5 NIH supported VTEUs**

U MD

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Background

- **Hib vaccines and DTaP vaccines were evaluated with concurrent OPV in pre-licensure studies**
- **No studies had been published comparing the immune responses to Hib and DTaP when co-administered with IPV vs. OPV**

Study Design

<u>Group</u>	<u>2 mo.</u>	<u>4 mo.</u>	<u>6 mo.</u>
A	OPV+DTaP+PRP-T	OPV+DTaP+PRP-T	OPV+DTaP+PRP-T
B	OPV+DTaP/PRP-T	OPV+DTaP/PRP-T	OPV+DTaP/PRP-T
C	IPV+ DTaP/PRP-T	IPV+ DTaP/PRP-T	OPV+DTaP/PRP-T
D	IPV+ DTaP/PRP-T	IPV+ DTaP/PRP-T	IPV+ DTaP/PRP-T

Vaccines

DTaP :

Tripedia*

PRP-T:

ActHIB*

DTaP / PRP-T:

TriHIBit*

IPV:

IPOL*

OPV:

Orimune

***Manufactured and donated by Adventis Pasteur**

Injection Sites

Right Thigh

PRP-T

IPV

Left Thigh

DTaP

DTaP/PRP-T

Primary Objective

To confirm that the experimental treatment arms (B, C, D) are non-inferior to the standard arm (A) with respect to the proportion of children achieving protective levels of Ab to polioviruses 1, 2, 3; tetanus Toxin; diphtheria toxin; and Hib.

Sample Size for Establishing Equivalence

- Based on proportion of children achieving $\geq 1.0 \mu\text{g/ml}$ anti-PRP
- Experimental arm equivalent to reference arm if upper bound of 95% CI for difference in proportion of reference arm – experimental arm $\leq 10\%$
- 90% power if 95% of children attain protective levels

Number of Subjects

<u>Group</u>	<u>ITT*</u>	<u>PP</u>
A	123	112
B	132	125
C	133	118
D	130	118

* # enrolled who had a post-dose 3 anti-PRP result

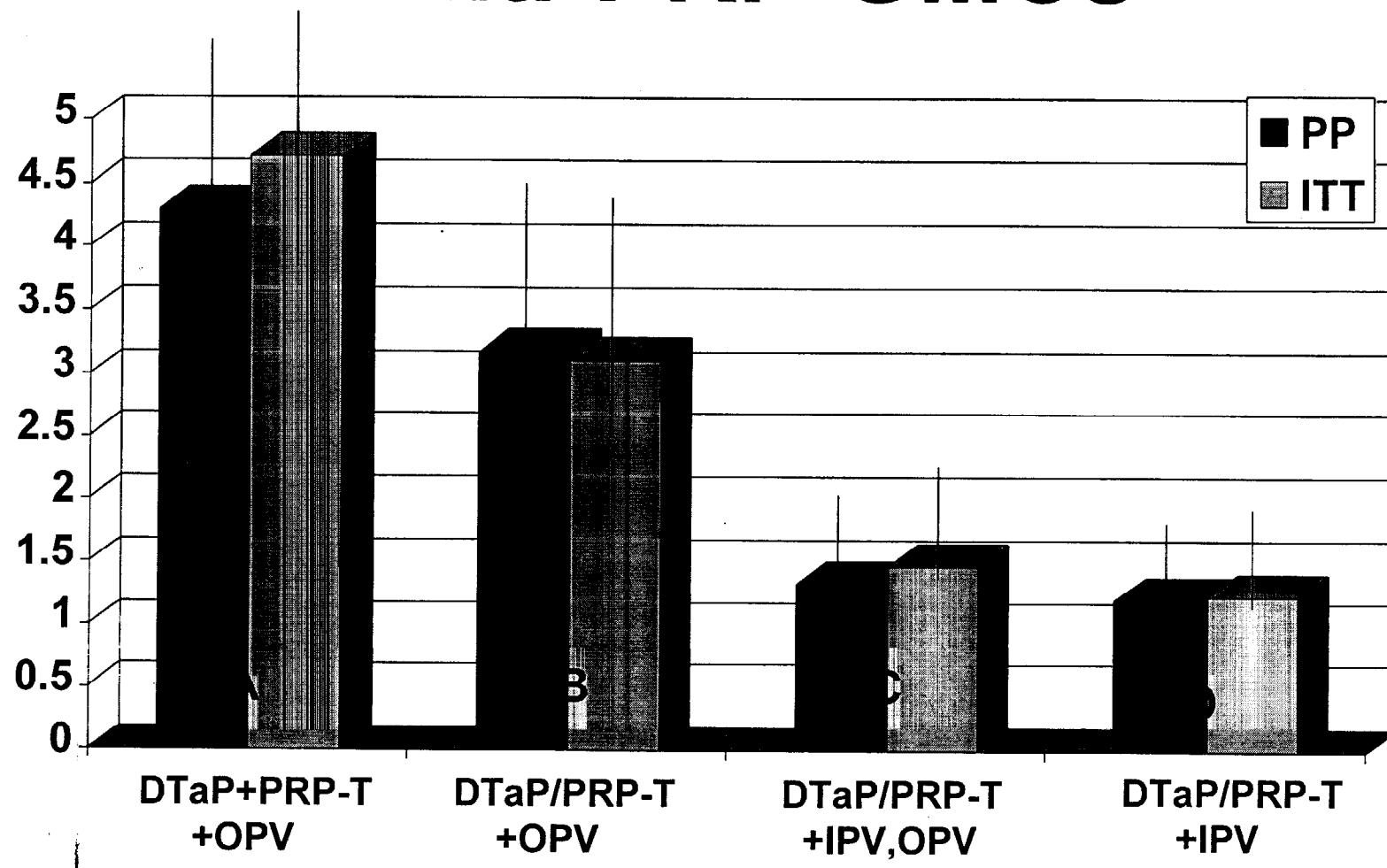
Serology

Blood drawn 1 month after dose 3

<u>Antibodies measured to :</u>	<u>Assay</u>
PRP	RIA*
PT	ELISA†
FHA	ELISA†
TT	ELISA†
DT	Neutralization†
Polio types 1, 2, 3	Neutralization†

*Adventis Pasteur, USA; †G. Losonsky

Anti-PRP GMCs



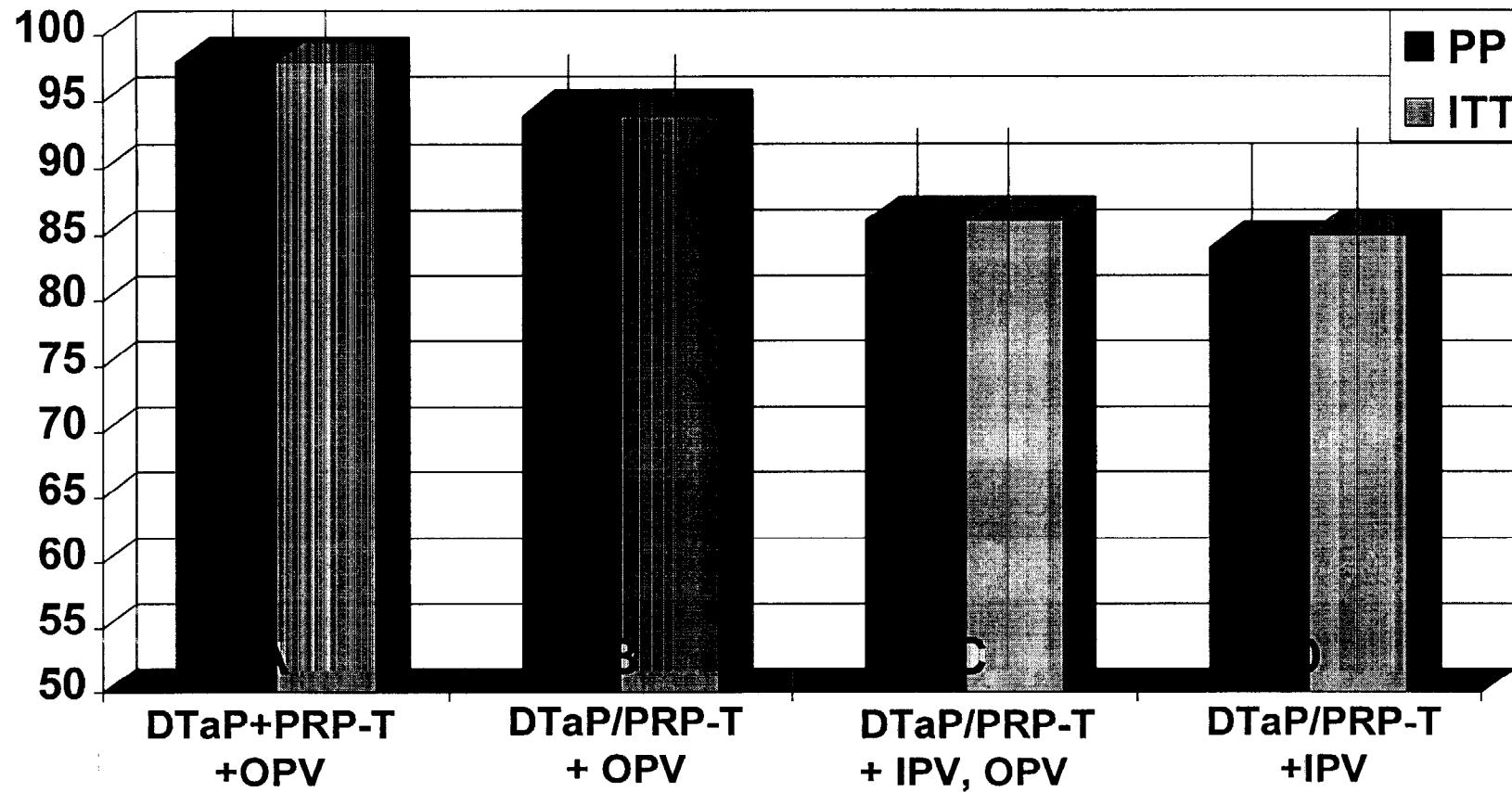
PP: A vs. B, P=0.14
A vs. C, P=.0001
A vs. D, P=.0001

B vs. C, P=.0001
B vs. D, P=.0001

ITT: A vs. B, P=0.06
A vs. C, P=.0001
A vs. D, P=.0001

B vs. C, P= .0005
B vs. D, P=.0001

% Anti-PRP \geq .15 $\mu\text{g/ml}$



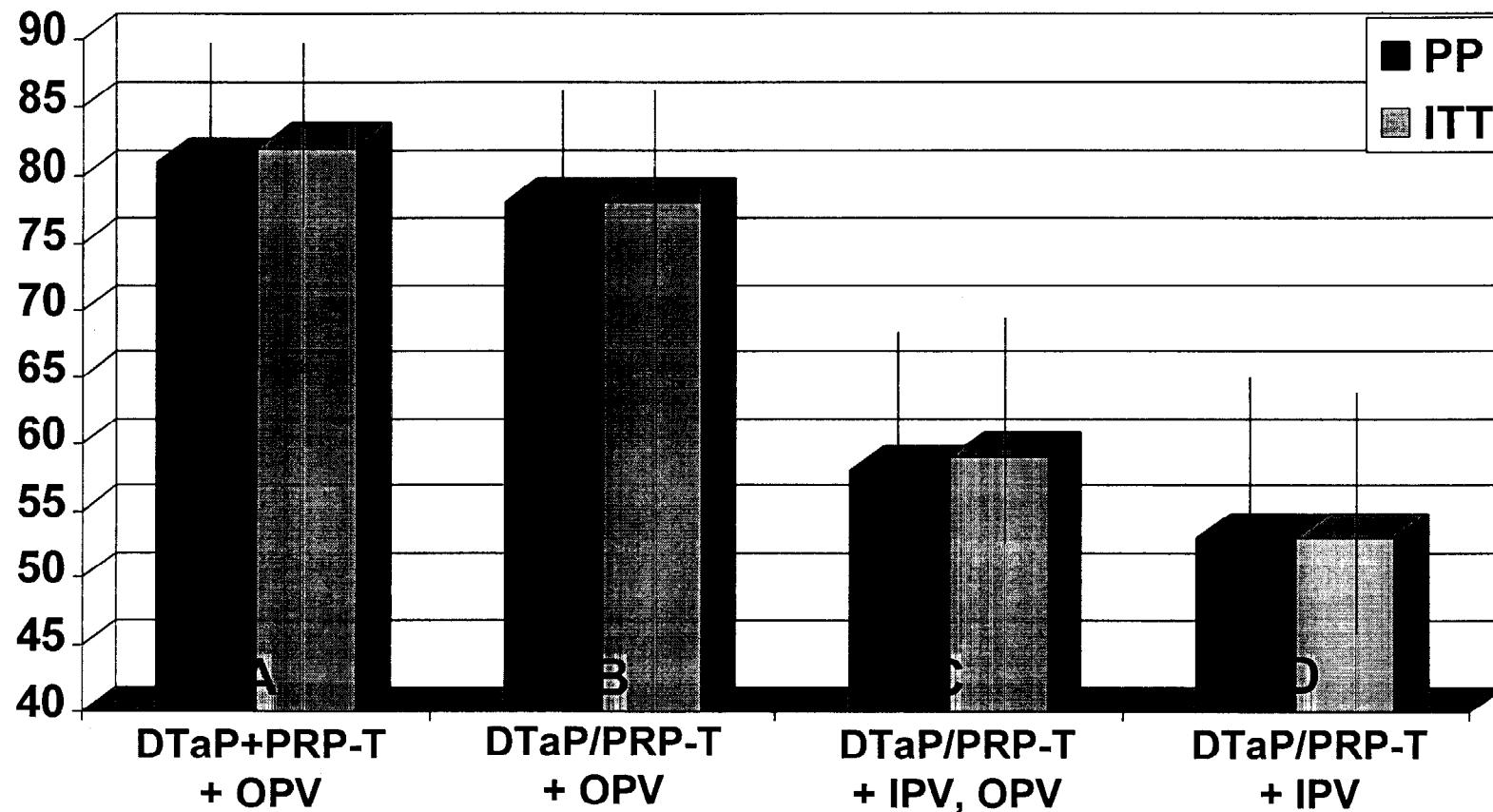
PP: A vs B, P=.11
A vs C, P=.0005
A vs D, P=.0001

B vs C, P=.06
B vs D, P=.02

ITT: A vs B, P=.11
A vs C, P=.0003
A vs D, P=.0001

B vs C, P=.06
B vs D, P=.03

% Anti-PRP \geq 1.0 $\mu\text{g/ml}$



PP: A vs B, P=.63

A vs C, P=.0001

A vs D, P=.000007

B vs C, P=.0006

B vs D, P=.00004

ITT: A vs B, P=.44

A vs C, P=.00007

A vs D, P=.00001

B vs C, P=.001

B vs D, P=.00003

Differences in Proportions (95% CI) (Intent to Treat)

Comparison	$\geq .15\mu\text{g/ml}$	$\geq 1.0 \mu\text{g/ml}$
A vs B ($P_B - P_A$)	-4.4% (-9.1, 0.2)	-4.1% (13.9, 5.7%)
A vs C ($P_C - P_A$)	-11.9% (-18.1, -5.7)	-22.7% (-33.5, -12.0)
A vs D ($P_D - P_A$)	-13.0% (-19.5, -1.2)	-29.0% (-40.0, -18.1)
B vs C ($P_C - P_B$)	-7.5% (-14.6, -0.4)	-18.6% (-29.6, -7.7)
B vs D ($P_D - P_B$)	- 8.5% (-15.9, -1.2)	-25.0% (-36.1, -13.8)

Differences in Proportions (95% CI) (Per Protocol)

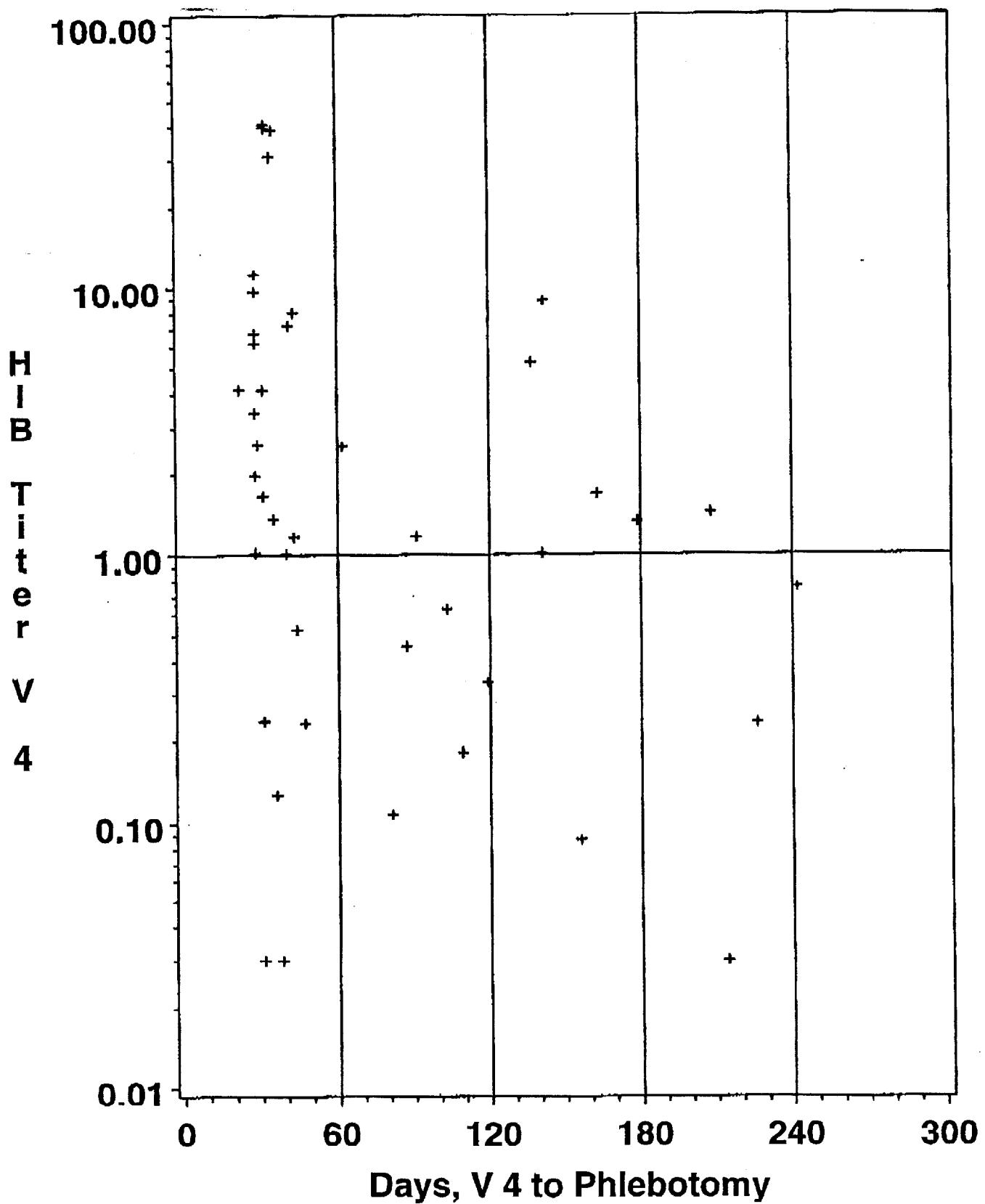
Comparison	$\geq .15\mu\text{g/ml}$	$\geq 1.0 \mu\text{g/ml}$
A vs B ($P_A - P_B$)	- 4.6% (-9.6, 0.3)	- 2.9% (-13.1, 7.4)
A vs C ($P_A - P_C$)	- 12.6% (-19.4,-5.8)	- 23.6% (-35.1,-12.1)
A vs D ($P_A - P_D$)	- 14.3% (-21.4,-7.2)	- 27.9% (-39.4,-16.3)
B vs C ($P_B - P_C$)	- 8.0% (-15.7,-.4)	- 20.8% (-32.2, -9.3)
B vs D ($P_B - P_D$)	- 9.7% (-17.6,-1.8)	- 25.0% (-36.6, -13.5)

Results by Site

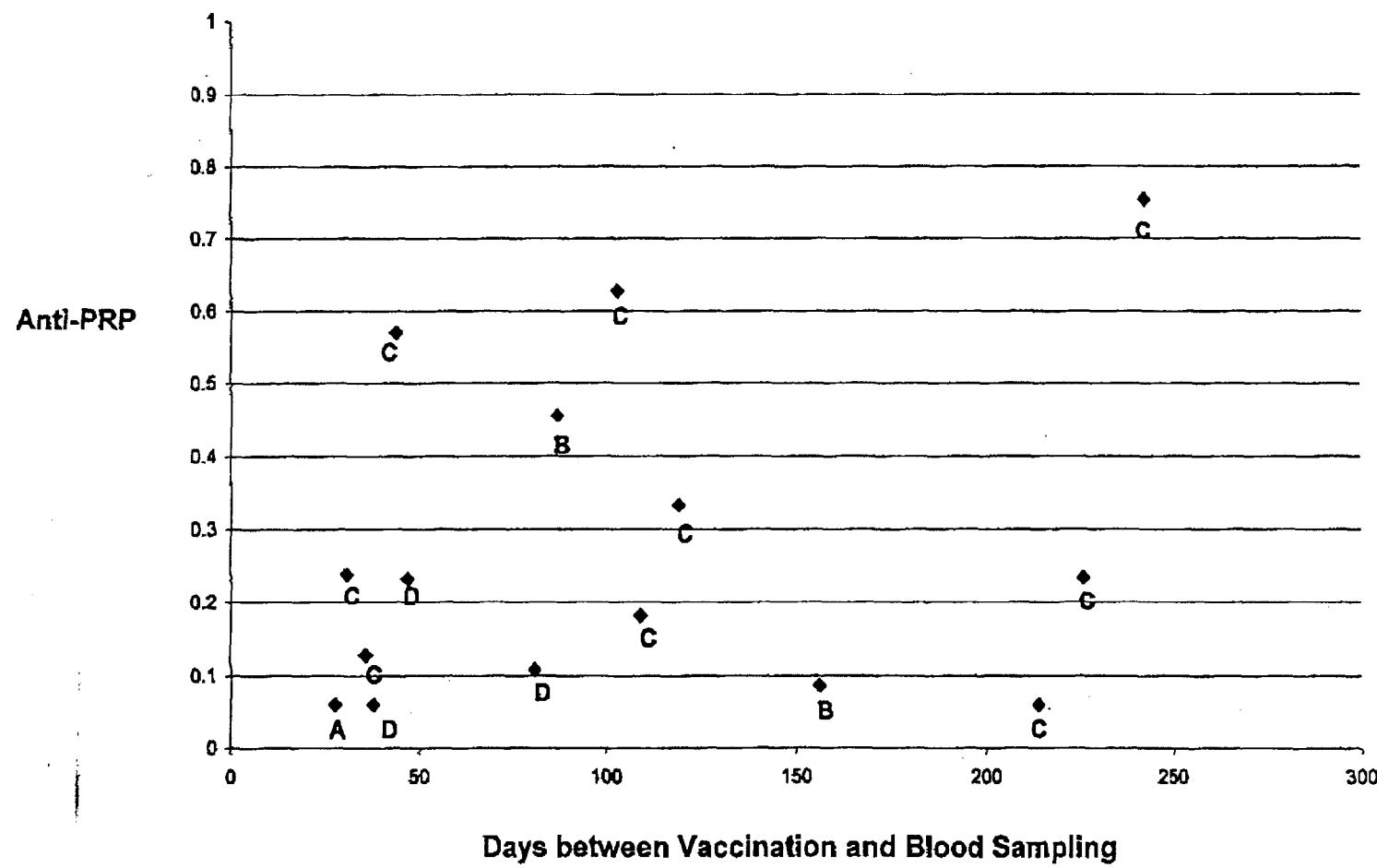
- The overall post-dose 3 anti-PRP results did not differ by study site
- Sample sizes inadequate to analyze differences between sites

Post-Dose 4 Anti-PRP Results

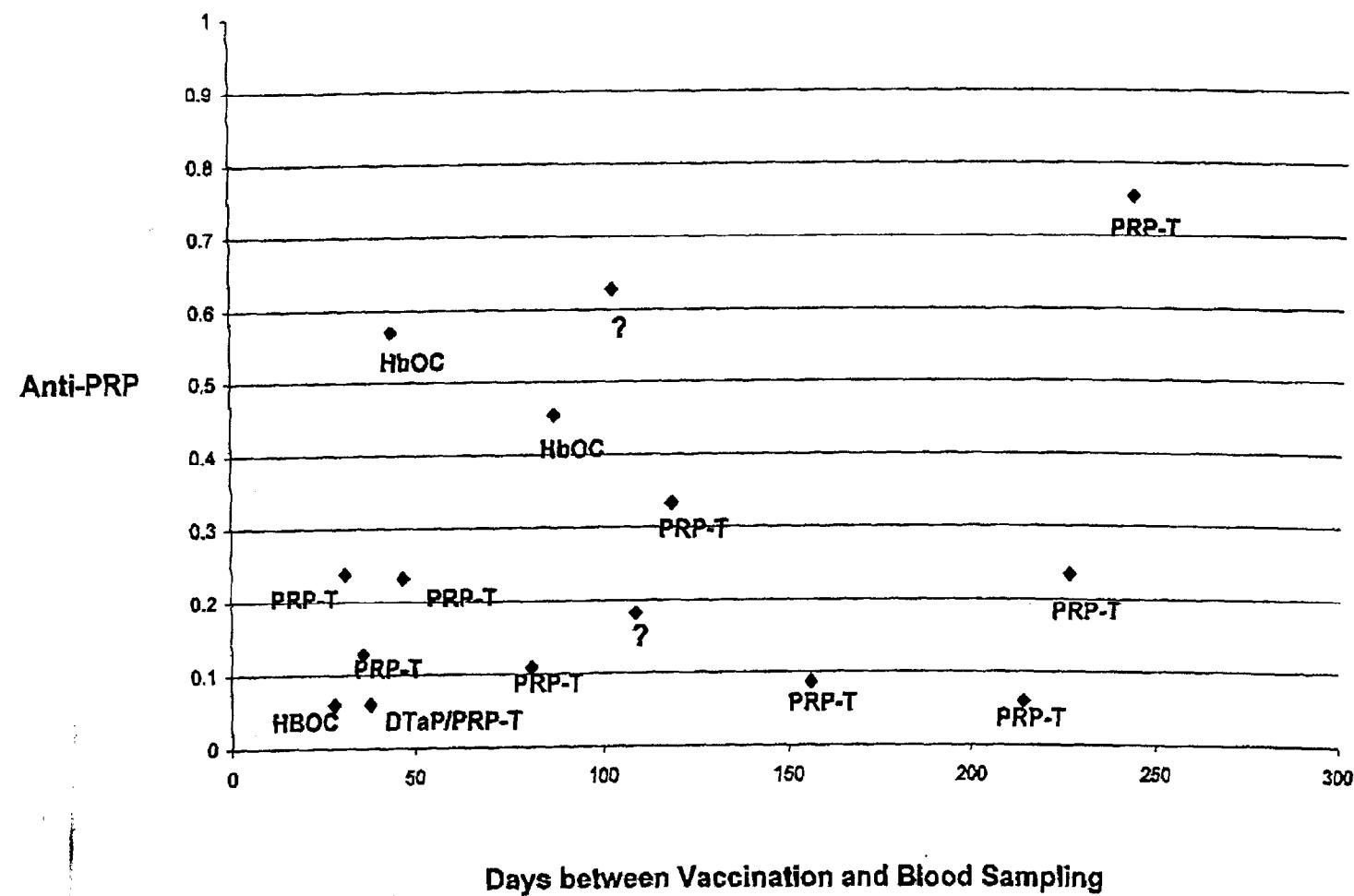
- 47 children had post dose 3 anti-PRP $\leq .15 \mu\text{g/ml}$
- Blood obtained on 43 between 1- 8 mo. post-dose 4



Primary Series Vaccine Group



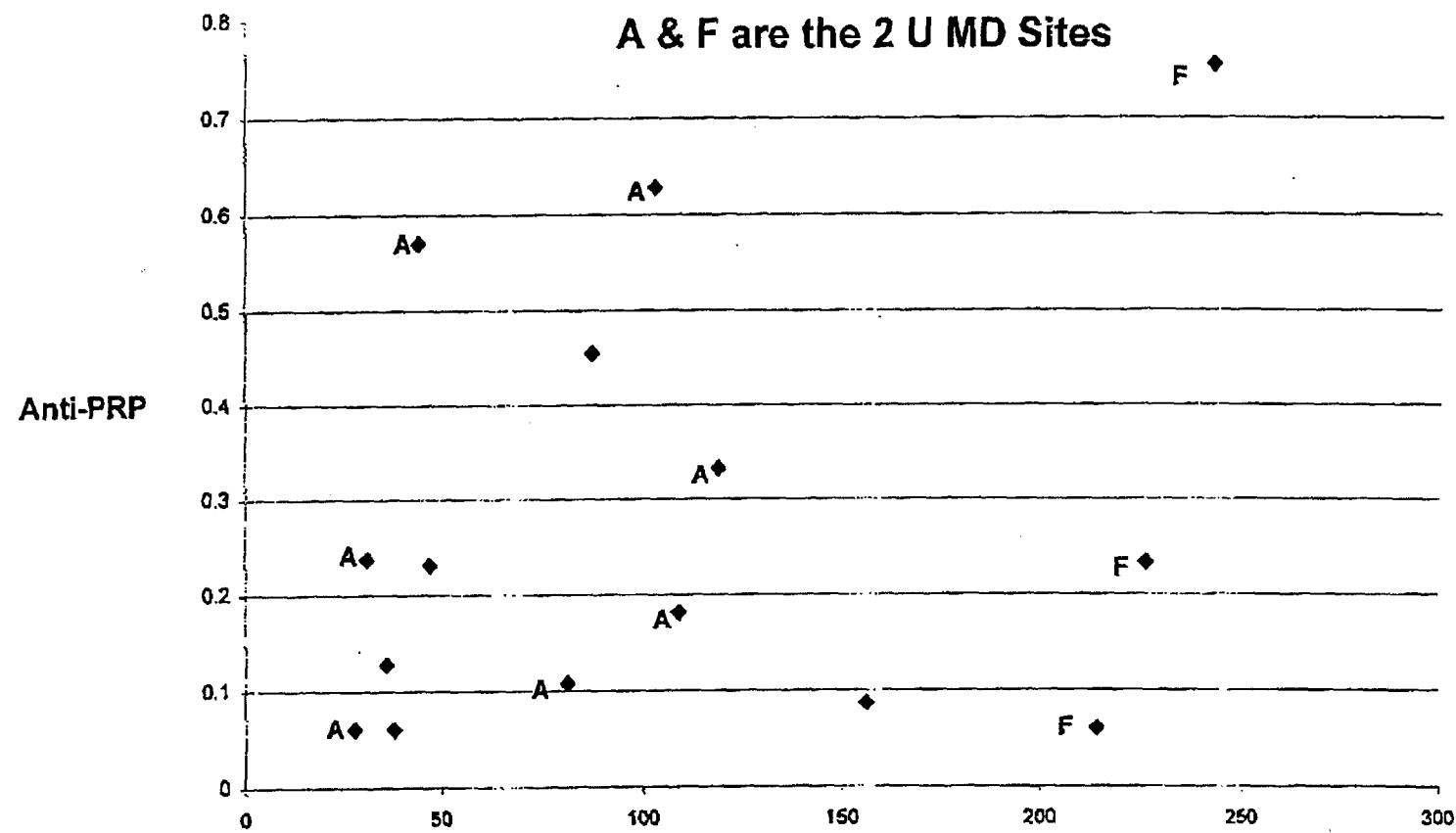
Hib Vaccine Received as 4th Dose



Time Between Dose 4 and Blood by Site

<u>VTEU</u>	# Subj.	<u>Days from Vaccination to Blood</u>			
		<u>Min</u>	<u>Max</u>	<u>Mean</u>	<u>Median</u>
Baylor	11	22	179	64	35
Gamble	7	31	208	69	43
Rochester	5	28	34	29	28
St. Louis	5	28	43	37	40
Maryland	15	28	242	121	119

Anti-PRP Level vs. Time from Vaccination



Days between Vaccination and Blood Sampling

Conclusion

**In this trial, concurrent IPV
interfered with the primary anti-PRP
response to this lot of this
DTaP/PRP-T vaccine**